Inhibition of disease flare with diethylstilbestrol diphosphate and chlormadinone acetate administration for two weeks prior to slow-releasing leuprolide acetate in prostatic cancer patients

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INHIBITION OF DISEASE FLARE WITH DIETHYLSTILBESTROL DIPHOSPHATE AND CHLORMADINONE ACETATE ADMINISTRATION FOR TWO WEEKS PRIOR TO SLOW-RELEASING LEUPROLIDE ACETATE IN PROSTATIC CANCER PATIENTS

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To determine whether administration of estrogen or gestagen prior to luteinizing hormone-releasing hormone (LH-RH) agonist prevents disease flare in prostate cancer patients, we pretreated the patients with either diethylstilbestrol diphosphate (DES-P) 300 mg daily (N=17) or chlormadinone acetate (CMA) 100 mg daily (N=16) or none (N=16) for two weeks before the initial injection of leuprolide acetate (L). Blood samples for prostatic specific antigen (PSA), testosterone (T), and luteinizing hormone were collected before CMA and DES-P administration, before and at 2, 7, 14, 28, 56, and 84 days after the first administration of leuprolide.

The treatment with DES-P and CMA prior to LH-RH agonist induced an early decline of PSA. The mean PSA level showed no significant secondary rise in those patients with pretreatment after L administration. In the patients pretreated with DES-P or CMA, the mean serum T level never exceeded the pretreatment baseline after L administration. On the other hand, in the patients without DES-P or CMA, both serum T and PSA levels increased after the first administration of L.

These results clearly demonstrate that pretreatment with DES-P 300 mg daily or CMA 100 mg daily for 2 weeks is quite effective to prevent disease flare after the first administration of L in patients with prostatic cancer.

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Key words: Prostate cancer, Disease flare, LH-RH analogue, Chlormadinone acetate, Diethylstilbestrol diphosphate

INTRODUCTION

Androgen suppression has been considered to be quite effective for treatment of advanced prostatic cancer and orchidectomy or anti-androgenic therapies are extensively performed. But the use of female sex hormones is associated with adverse effects on the cardiovascular system. Recently, luteinizing hormone-releasing hormone agonist (LH-RH agonist) has become widely used not only because its effects are equal to or greater than that of female sex hormones[1,2], but also because the use of LH-RH agonist scarcely induces cardiovascular complications or gynecomastia. However, flare-up symptoms and elevation of tumor marker may follow in 5–10% of patients[3–5] after the initial injection of LH-RH agonist inevitably associated with elevation of serum LH and testosterone. Although these symptoms are usually transient and are observed only after the first injection of agonist, patient demise has been reported from sudden death[6] Since Trachtenberg reported that flare-up can be suppressed by preadministration of estrogen[7], various therapies to suppress flare-up have been attempted[5,8–10]. In the present prospective randomized study, we compared the anti-flare up effects of diethylstilbestrol diphosphate (DES-P) and chlormadinone acetate (CMA) in the LH-RH agonist therapy of prostate cancer patients.

PATIENTS AND METHODS

This study was a prospective randomized clinical trial.

Sixty-one subjects with untreated prostatic cancer were registered in this study. The stage of subjects ranged from B1 to D2: the grade, poor to well-differentiated: and the performance status (P.S.) 0–3. The patients were randomized into three groups: Patients in group L received 3.75 mg slow-releasing

leuprolide acetate (L) subcutaneously every four weeks for 12 weeks; Patients in group L+DES-P received DES-P 300 mg daily, beginning at two weeks before the initial injection of L and continued over the 12-week L treatment: Patients in group L+CMA received the same protocol as patients in group L+DES-P except that CMA, 100 mg daily, was used instead of DES-P (Fig. 1). These daily doses are commonly used for prostate cancer in Japan.

Blood samples for determination of prostatic specific antigen (PSA) were collected before DES-P and CMA administration, before and at two days the onset of therapy as well as at one, two, four, eight and twelve weeks after the first administration of leuprolide. At the same time, serum LH and testosterone were measured by radioimmunoassay.

All patients were monitored carefully at each visit to make sure they took their medication and to check for any change in subjective and objective signs and symptoms as well as in laboratory findings.

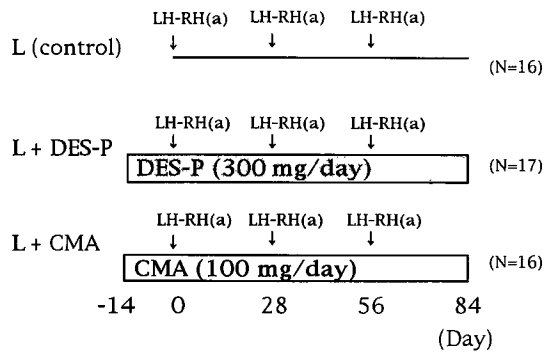

Fig. 1. Study protocol. L & LH-RH (a): leuprolide acetade 3.75 mg, DES-P: diethylstilbestrol diphosphate, CMA: chlormadinone acetate.

RESULTS

Out of 61 patients registered, 55 patients were enrolled into either the L, L+DES-P or L+CMA protocol. Two patients were not qualified for the study because they did not receive treatment according to protocol, and four dropped out during the study (three elected to discontinue treatment, one died of an unrelated condition). There were no statistically significant differences in the patient's profile among the three groups (Table 1).

1) Changes in serum hormone and tumor marker levels

I. LH

The per cent changes in the serum LH level from

Table 1. Patient profile

		L (N=16)	L+DES-P (N=17)	L+CMA (N=16)	
Age	60–69	2	2	2	6
	70–79	9	10	7	26
	80–	5	5	7	17
	Mean±SD	77.1±6.2	76.6±5.5	77.8±7.7	77.1±6.4
Stage	B1	1	2	4	7
	B2	1	3	1	5
	C	11	6	3	20
	D1	0	0	1	1
	D2	3	6	7	16
Differentiation	well	2	2	5	9
	moderate	9	12	6	27
	poor	5	3	5	13
P.S.	0	7	10	10	27
	1	7	5	3	15
	2	1	0	3	4
	3	1	2	0	3
	4	0	0	0	0
Serum Hormone	Testosterone (ng/ml)	5.38±2.82	3.48±1.35	4.35±1.27	
	LH (mIU/ml)	15.7±11.2	14.0±13.9	11.0±7.2*	
Tumor Marker	PSA (ng/ml)	83.6±98.1	212.3±458.3	520.9±1,793.3	
Metastasis	None	12	11	8	
	Bone	2	6	7	
	Lymph node	1	1	2	
	Lung	1	1	0	
	Others	1	0	0	

L: leuprolide acetate, DES-P: diethylstilbestrol diphosphate, CMA: chlormadinone acetate)

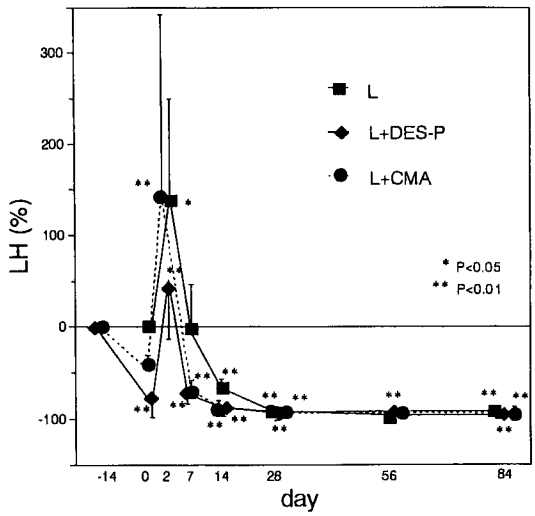

Fig. 2. Rate of change in blood luteinizing hormone (LH) level from baseline (level before administration) on the day of administration of leuprolide, and 2 days, one, 2, 4, 8 and 12 weeks after administration. The levels were analyzed by paired t-test, including the level before administration.

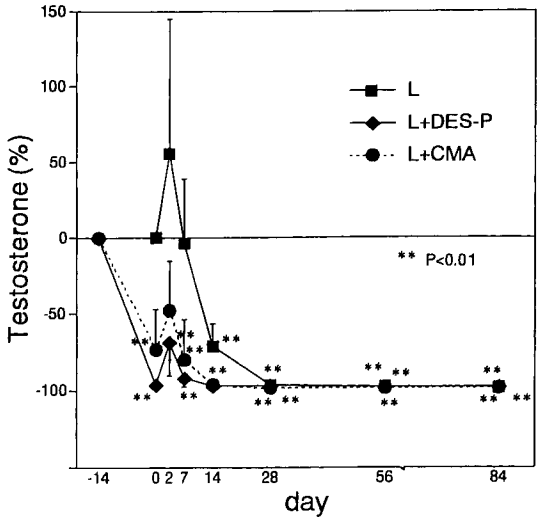

Fig. 3. Rate of change in blood testosterone level from baseline (level before administration) on the day of administration of leuprolide, and 2 days, one, 2, 4, 8 and 12 weeks after administration. The levels were analyzed by paired t-test, including the level before administration.

the baseline pretreatment level are shown in Fig. 2. In Groups L+DES-P and L+CMA, the serum LH level decreased during the two-week administration of DES-P and CMA. Although the LH surge on day 2 of leuprolide administration was to the same degree in the L, L+DES-P, and L+CMA group, but occurred from the levels already suppressed in the latter two groups. Subsequently, the LH level rapidly decreased to the level significantly lower ($p<0.01$) than pretreatment level within two weeks in all three groups.

II. Testosterone

The serum testosterone level was elevated from the baseline on day 2 of leuprolide administration and subsequently decreased in Group L. In Groups L+DES-P and L+CMA, the serum testosterone levels significantly decreased with the precedent administration of DES-P and CMA, from 338 ng/dl to 11.4 ng/dl ($p<0.01$) and from 447 ng/dl to 100 ng/dl ($p<0.01$), respectively. The blood testosterone levels increased from the suppressed baseline to 141 ng/dl in Group L+DES-P and 327 ng/dl in Group L+CMA on day two of the administration of leuprolide transiently, but decreased to the castrated level in two weeks (Fig. 3). In Groups L+DES-P and L+CMA, the magnitude of testosterone flare-up was small and the peak level did not exceed the pretreatment baseline.

III. Tumor marker

PSA level was slightly but not significantly elevated on day two of leuprolide administration in Group L. Thereafter, the levels decreased gradually to values significantly lower ($p<0.01$) than the pretreatment

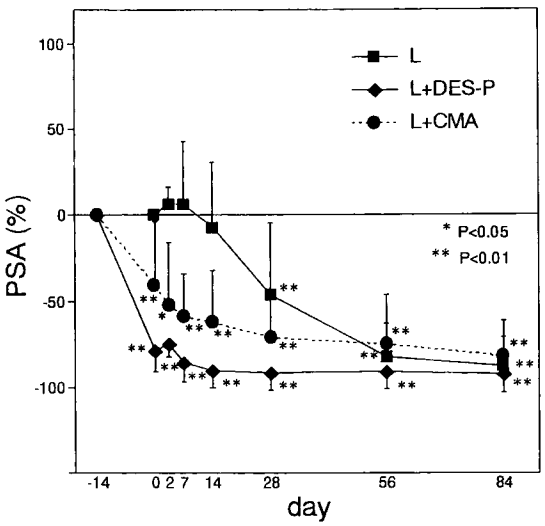

Fig. 4. Rate of change in blood prostate specific antigen (PSA) level from baseline (level before administration) on the day of administration of leuprolide, and 2 days, one, 2, 4, 8 and 12 weeks after administration. The levels were analyzed by paired t-test, including the level before administration.

levels in four weeks (Fig. 4). In Groups L+DES-P and L+CMA, PSA significantly ($p<0.01$) declined during the initial two-week administration of DES-P and CMA. No remarkable changes were observed even with leuprolide administration. After eight weeks of therapy with leuprolide, a significant decrease in tumor marker was observed in all three groups with no significant differences.

2) Adverse effects

The observed subjective and objective side effects

Table 2. Adverse effects

	L	L+DES-P	L+CMA	Total
N	17	19	19	55
Number of side effects	3	13	5	21
Sweating	0	1	1	2
Elevated s-ALP	0	1	0	1
Elevated s-GOT	1	0	1	2
Elevated s-GPT	1	0	1	2
Elevated triglyceride	1	1	1	3
Anemia	0	5	0	5
Leukocytosis	0	1	0	1
Hypoalbuminemia	0	1	0	1
Hyponatremia	0	1	0	1
Impotence	0	0	1	1
Gynecomastia	0	1	0	1
Heart failure	0	1	0	1

are shown in Table 2. None of them were serious. No side effects attributable to flare-up were obsurved in any group throughout this study.

DISCUSSION

This prospective randomized study apparently demonstrates that pretreatment of patients with DES-P (300 mg/day) as well as CMA (100 mg/day) for 2 weeks eliminate the disease flare associated with the initial injection of LH-RH agonist for the patients with prostate cancer.

It has been reported that leuprolide is quite effective for early treatment of prostatic cancer[11,12]. Although chronic treatment with LH-RH agonists achieves castration levels without side effects other than those related to hypogonadism, a limitation to their use alone for the treatment of prostatic cancer is the increase in serum androgens that lasts for about one week after the start of treatment with the risk of transient disease flare. The clinical course of some patients can be serious during a short period just after initiation of LH-RH agonist therapy[6] In the present study, we investigated the effects of leuprolide with and without the precedent administration of DES-P and CMA on prostate cancer.

Luteinizing hormone and testosterone rose rapidly two days after the administration of leuprolide in Group L. And PSA consequently rose but not significantly from day 2 to day 7 after leuprolide administration suggesting disease flare in Group L. It took 4 weeks until PSA decreased significantly in this group. On the other hand, in group L+DES-P and group L+CMA with the precedent administration of DES-P and CMA, respectively, the serum testosterone levels significantly decreased within the first two weeks of therapy. PSA in the group L+DES-P and L+CMA also decreased significantly in the first two weeks and no remarkable rise was observed by leuprolide administration although serum testosterone levels were slightly elevated after the first administration of leuprolide. The serum PSA levels suggest that precedent administration of DES-P (300 mg/day) or CMA (100 mg/day) for 2 weeks is quite sufficient to prevent disease flare after the first injection of leuprolide. Moreover, with pretreatment of DES-P or CMA, serum PSA levels were reduced more rapidly to adequate levels than those in Group L without pretreatment. In Group L patients, further 2 weeks are required to demonstrate low PSA levels as those in the other two groups presumably due to the initial rise in serum testosterone level.

Several attempts to suppress LH-RH analog flare-up have been reported with regard to type, dose and timing of the drug administered prior to LH-RH analogue. Stein et al.[8] reported that testosterone elevation was not adequately suppressed despite diethylstilbestrol (DES) at a dose of 3 mg/day starting one week before leuprolide administration. On the other hand, Kreis et al.[9] reported that testosterone elevation was completely suppressed by administration of DES at a dose of 3 mg/day starting 4 weeks before administration of goserelin acetate (Zoladex), although LH elevation was not significantly suppressed. These reports are not entirely comparable because the patient's background and species of LH-RH analogue are different. However, it is suggested that the inhibitory effect of DES on testosterone flare differs with the duration of the precedent DES administration. According to Bruchovski et al.[10], flare up of testosterone and tumor markers could be completely suppressed by precedent administration of cyproterone acetate and a small dose of DES, 4 weeks prior to administration of LH-RH analog, goserelin acetate. As shown in this study, even after the preadministration of DES-P and CMA with daily doses commonly used in Japan, LH surges and subsequent rise in serum testosterone after the first leuprolide acetate administration did occur. To prevent disease flare, complete suppression of PSA should be achieved before the initial injection of LH-RH analogue. In this respect, 100 mg/day of CMA appears to be less effective than 300 mg/day of DES-P at day 0. However, PSA levels in group L+CMA gradually decreased after L administration although testosterone transiently rose at day 2. These results suggest the anti-androgenic effects of CMA as well as negative effect on hypothalamus or pituitary gland. Schulze et al.[5] reported that precedent administration of nonsteroidal antiandrogen flutamide one week prior to goserelin acetate (Zoladex), which does not suppress LH nor testosterone level, also exerted considerable anti-flare up effects with regard to prostatic acid phosphatase levels probably due to anti-androgenic effect at receptor level. Precedent administration of estrogen or antiandrogen could be validated for the anti-flare-up effect as well as for

earlier suppression of tumor markers.

In the present study, the PSA levels were not significantly different among the three groups of patients at 12 weeks of therapy. Whether the transient disease flare affects the prognosis of prostate cancer patients remains to be elucidated. Further long-term follow up of these patients is ongoing.

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和文抄録

前立腺癌の LH-RH アゴニストによる治療における，ホスフェストロールおよびクロルマジノンによるフレアー現象の抑制効果について

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三浦　　猛，近藤猪一郎，原田　昌興

LH-RH アゴニスト投与によるフレアー現象を抑制する目的で，アゴニスト投与2週間前よりエストロゲンあるいはゲスターゲンを投与した．前立腺癌患者でのこれらの薬剤の効果につき比較検討した．未治療前立腺癌患者を無作為に3群に分けた．ホスフェストロール 300 mg/day（N＝17），クロルマジノン 100 mg/day（N＝16），無治療（N＝16）を LH-RH アゴニスト初回投与の2週間前より開始した．LH，テストステロン，PSA 値を定期的に測定した．ホスフェストロール，クロルマジノンの前投与により PSA は早期に低下した．テストステロンの平均値はホスフェストロール，クロルマジノンの前投与群で，アゴニスト投与後も治療前の値を越えることはなく，PSA 平均値も前投与群ではアゴニスト投与後も有意の上昇を認めなかった．一方，前投与を行わなかった群では初回のアゴニスト投与により一過性にテストステロンおよび PSA 平均値は治療前値よりも上昇した．以上の結果よりホスフェストロール 300 mg/day，クロルマジノン 100 mg/day の2週間前投与は，初回 LH-RH アゴニスト投与後のフレアー現象に対しきわめて有用であることが明らかとなった．

（泌尿紀要 **46**：531-536，2000）